REMARKS

Claims 1-2 and 4-41 are pending, claim 3 having been previously canceled by applicants. Applicants acknowledge with appreciation the Examiner's withdrawal of the objections to the drawings and to the specification as set forth in the previous Office Action dated November 7, 2005. Applicants also acknowledge with appreciation the Examiner's withdrawal of certain claim rejections under 35 U.S.C. §112, 35 U.S.C. §102, and 35 U.S.C. §103. In the Action under reply, the claims have been rejected as follows:

(1) claims 13-15 are rejected under 35 U.S.C. §112, second paragraph, as indefinite;

(2) claims 1-2, 6, 10, 16, and 34 are rejected under 35 U.S.C. §102(b) as anticipated by Penners et al., US 6,306,439, ("Penners");

(3) claims 12-31, 35, 37-38, and 40-41 are rejected under 35 U.S.C. §103(a) as unpatentable over Kim et al., US 5,455,044 ("Kim") in view of Penners;

(4) claim 11 is rejected under 35 U.S.C. §103(a) as unpatentable over Kim in view of Penners and further in view of Chen et al., *Proc. Nat. Acad. Sci.*, 2002, 99(13), 9031-9036 ("Chen");

(5) claim 32 is rejected under 35 U.S.C. §103(a) as unpatentable over Kim in view of Penners, further in view of Chen, and further in view of Hatcher et al., *Soc. For Neurosciences*, 19th Annual Meeting, Abs. #236.4, Oct. 23-28, 1999 ("Hatcher"); and

(6) claims 36 and 39 are rejected under 35 U.S.C. §103(a) as unpatentable over Kim in view of Penners, and further in view of Russell et al. *Bone Marrow Transplantation*, 1999, 24, 1177-1183 ("Russell").

The rejections and objections are overcome in part by the amendments made herein, and are otherwise traversed for at least the reasons set forth below.

Claim Amendments

Claim 1 has been amended to recite that the composition comprises a plurality of polymer particles. Support for this amendment may be found, for example, on page 2, lines 29-30 of the original specification. Claim 1 has also been amended to recite that each of the polymer particles is 1-100 μm in size. Support for this amendment can be found on page 29, line 8 of the original specification. Claim 10 has been amended to fix a typographical error - a space has been added between "claim" and "1." Claim 12 has been amended to recite a plurality of first polymeric

particles and a plurality of second polymeric particles. Support for this amendment may also be found, for example, on page 2, lines 29-30 of the original specification. Claims 13-15 have been amended to reflect the amendment to claim 12. Claim 22 has been amended to recite that the composition comprises a plurality of polymer particles. Accordingly, no new matter is added by these amendments.

Rejection under 35 U.S.C. §112, second paragraph

Claims 13-15 stand rejected under 35 U.S.C. §112, second paragraph, as indefinite, the Examiner contending that the recited limitation "the ratio" lacks antecedent basis. This rejection is overcome by the amendments made herein.

According to MPEP §2173.05(e) "[i]nherent components of elements recited have antecedent basis in the recitation of the components themselves." One of ordinary skill in the art would immediately recognize that, in a composition having two components (e.g., the composition according to claim 12, which comprises a plurality of first polymeric particles and a plurality of second polymeric particles), a ratio between the amount of the first component and the amount of the second component is intrinsically present. Accordingly, applicants respectfully request withdrawal of the rejection.

Rejection under 35 U.S.C. §102(b)

Claims 1-2, 6, 10, 16, and 34 stand rejected under 35 U.S.C. §102(b) as anticipated by Penners. The Examiner states that Penners discloses a composition that meets the limitations of the rejected claims. This rejection is traversed.

With the amendments made herein, claim 1 and claims depending therefrom require a biocompatible composition "comprising a *plurality* of polymer particles..." (emphasis added). Penners does not disclose such a composition. Even considering Penners in the light most favorable to the Examiner's position, Penners discloses a hydrated gel with a gas incorporated therein. Such a hydrated gel, however, is not a plurality of polymer particles, as required by the pending claims. Indeed, the very nature of a hydrated gel as described in Penners indicates that such a composition is a single gelatinous mass. The Examiner points out that the physical form of the compositions described in Penners may be selected from the group consisting of tablets,

capsules, granules and pellets (col. 5, lines 33-34). At no point, however, does Penners suggest preparation of a composition comprising a plurality of polymer particles.

Furthermore, claim 1 (as amended) requires that each of the polymer particles is 1-100 μm in size. As mentioned previously, Penners discloses compositions that may be in the form of tablets, capsules, and granules or pellets. However, Penners does not disclose that such tablets, capsules, and granules or pellets may be 1-100 μm in size. In fact, at no point does Penners disclose particles that are in the range of sizes of the instant claims.

Because Penners does not disclose a composition comprising a *plurality* of polymer particles, each of which is 1-100 μm in size, the disclosure of Penners does not anticipate the instant claims. Applicants respectfully request withdrawal of the rejection.

First rejection under 35 U.S.C. §103(a)

Claims 12-31, 35, 37-38, and 40-41 stand rejected under 35 U.S.C. §103(a) as unpatentable over Kim in view of Penners. The Examiner states that Kim lacks the teachings of a specific buoyancy agent, and that Penners provides such teachings. This rejection is traversed.

The Examiner has failed to meet the requirements for a *prima facie* case of obviousness over the reference. The MPEP (§2142) lists three criteria, all of which must be met in order for there to be a *prima facie* case of obviousness:

> First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

The Examiner contends that it would have been obvious to a person of ordinary skill at the time of the instant invention to combine the teachings of Kim and Penners (Action at page 9). Furthermore, the Examiner states that Penners teaches that the gas-forming substances in his composition evolve non-toxic gases upon contact with water (Action at page 10).

However, in making these statements the Examiner overlooks the fact that, in addition to the gases generated in the reaction of hydrogen carbonates with water, toxic byproducts are also generated. One of ordinary skill in the art to which the invention pertains would recognize that compositions that contain hydrogen carbonates, such as those described in Penners, decompose in water to form carbon dioxide *and hydroxide ion* (i.e., OH^-). In summary, and as supported by

the arguments presented below, one of ordinary skill in the art would not have been motivated to combine the teachings of Kim with the teachings of Penners.

The compositions described by Penners and cited by the Examiner are clearly not compositions that are suitable for administration to the cerebrospinal fluid of a subject. In particular, Penners discusses the addition of gas-forming agents to the compositions, and gives the example of hydrogen carbonates such as sodium hydrogen carbonate (col. 5, lines 5-9). Although the gas-forming agents suggested by Penners form "non-toxic gases" (line 8), such agents also form non-gaseous byproducts that are not desirable in the cerebrospinal fluid of a subject. In particular, when exposed to aqueous environments, hydrogen carbonates form CO_2 as well as *hydroxide ion* (i.e., OH^-). Generation of OH^- in the CSF, as would occur upon administration of compositions such as those described in Penners to the CSF of a patient, would have the effect of changing the pH of the CSF. The detrimental side-effects of pH changes in the CSF of a patient clearly indicate that the compositions of Penners are not suitable for administration to the CSF of a patient.

Hydroxide ion is a strongly basic substance, and may be a non-toxic byproduct in compositions intended for administration to the gastrointestinal tract (such as those described in Penners). In fact, it is common practice to administer to the gastrointestinal tract of a patient a composition comprising a hydrogen carbonate (e.g., antacid medications such as common baking soda), and the OH^- generated in the reaction of such compositions with water has a variety of beneficial effects. An increase in pH is often a desirable effect of such compositions, as the pH of the gastrointestinal tract may be upset by a variety of factors (such as the digestion of spicy foods, genetic traits, etc.). The gastrointestinal tract is subjected to a wide variety of external stimuli, most notably due to the solids and liquids that pass through the tract in the course of normal metabolic regulation (e.g., the process of eating and drinking common to most animals). Accordingly, the gastrointestinal tract is capable of tolerating wide variations in pH. For example, the pH of the human stomach may vary from 1-4 under normal conditions. The compositions of Penners are intended for administration to the gastrointestinal tract (see Abstract of Penners); accordingly, basic byproducts such as hydroxide ions are not only innocuous for such compositions, but may indeed have beneficial side effects (such as antacid properties).

In contrast to the gastrointestinal (GI) tract, the central nervous system (CNS) of a patient is quite sensitive to external stimuli. Under normal circumstances, the CNS contains

cerebrospinal fluid (CSF), which is closely regulated to avoid the introduction of toxic substances. The CSF is typically maintained at a pH of about 7.35; unlike for the GI tract, wide variation in pH of the CSF is uncommon and has the potential of being severely harmful. Therefore, although carbon dioxide may not be toxic to the CNS, as is evident by the instant specification, many substances that could be tolerated by the GI tract are not appropriate for administration to the CSF. At least because of the differences between the GI tract and the CSF with respect to pH regulation, one of ordinary skill seeking compositions suitable for administration to the CSF would not look to art that describes compositions suitable for administration to the GI tract. In fact, the skilled artisan would recognize that the compositions of Penners generate potentially toxic substances (i.e., OH^-) when contacted with aqueous solutions such as the CSF. Thus, not only is there a lack of motivation for the skilled artisan to combine the teachings of Penners with those of Kim, but such a combination would in fact be discouraged based on the undesirable byproducts formed by the compositions of Penners.

To summarize, the skilled artisan would not look to Penners, which is directed to compositions suitable for administration to the gastrointestinal tract, in order to modify the teachings of Kim, which is directed to compositions suitable for administration to the CSF. The skilled artisan would not be motivated to modify the compositions of Kim as suggested by the Examiner, but would in fact be discouraged from such modifications.

In addition, assuming *arguendo* that the references were combined, Penners and Kim together do not teach the claimed invention. Kim states that "[m]aterials used in the preparation of dispersion systems are typically sterilizable via filter sterilization, *nontoxic*, and biodegradable..." (col. 3, lines 37-39, emphasis added). However, as discussed above, the materials of Penners (i.e., hydrogen carbonates) release potentially toxic substances and would therefore not be suitable for the compositions disclosed in Kim.

For at least the foregoing reasons, the combination of Penners and Kim do not render obvious claims 12-31, 35, 37-38, and 40-41, and applicants respectfully request withdrawal of the rejection.

Second rejection under 35 U.S.C. §103(a)

Claim 11 stands rejected under 35 U.S.C. §103(a) as unpatentable over Kim in view of Penners and further in view of Chen. The Examiner states that both Kim and Penners lack the

teaching of a biocompatible composition wherein the therapeutic agent is selected from the group of inosine, citicholine, superoxide dismutase, and dextrophan, and that this deficiency is cured by the teachings of Chen (Action at page 13). This rejection is traversed.

The merits of the combination of Kim and Penners, as proposed by the Examiner, are discussed above. In summary, one of ordinary skill in the art would find no motivation to combine the teachings of Penners with Kim, at least for the reason that the compositions of Penners would generate byproducts that are potentially toxic to the CNS and are therefore unsuitable for administration to the CSF. In addition, as described above, the combination of Penners and Kim does not render the claims obvious.

Regardless of the therapeutic agents that are employed, the teachings of Chen do not provide the motivation that would be needed to combine the teachings of Kim with the teachings of Penners. Chen is directed to the effects of inosine on rats suffering from certain types of strokes. Chen does not address biocompatible compositions suitable for administration to the cerebrospinal fluid of a subject comprising a plurality of polymer particles, as claimed. Therefore, Chen does not address the deficiencies of either Kim or Penners, or the combination of Kim with Penners as described above, with respect to claim 1 (and claims dependent thereon, including claim 11). Any combination of Chen with Kim or Penners (or both) fails to teach the claimed invention; accordingly, applicants respectfully request withdrawal of the rejection.

Third rejection under 35 U.S.C. §103(a)

Claim 32 stands rejected under 35 U.S.C. §103(a) as unpatentable over Kim in view of Penners, further in view of Chen, and further in view of Hatcher. The Examiner contends that Kim, Penners, and Chen lack the teaching of a composition comprising both inosine and citicholine as therapeutic agents, and that this deficiency is cured by the teachings of Hatcher (Action at page 14). This rejection is traversed.

The merits of the combination of Kim, Penners, and Chen, as proposed by the Examiner, are discussed above. In summary, one of ordinary skill in the art would find no motivation to combine the teachings of Penners with Kim, at least for the reason that the compositions of Penners would generate byproducts that are potentially toxic to the CNS and are therefore unsuitable for administration to the CSF. Furthermore, Chen does not provide the motivation that would be required to combine the teachings of Kim with those of Penners.

Regardless of the therapeutic agents that are employed, the teachings of Hatcher do not provide the motivation that would be needed to combine the teachings of Kim with those of Penners and with those of Chen. Hatcher is directed to the neuroprotective effect of CDP-choline in hippocampal CA_1 region after transient ischemia of gerbils (see Abstract). Hatcher does not address biocompatible compositions suitable for administration to the cerebrospinal fluid of a subject comprising a plurality of polymer particles, as claimed. Therefore, Hatcher does not address the deficiencies of Kim, Penners, Chen, or any combination thereof, as described above, with respect to claim 12 (and claims dependent thereon, including claim 32). Accordingly, applicants respectfully request withdrawal of the rejection.

Fourth, rejection under 35 U.S.C. §103(a)

Claims 36 and 39 stand rejected under 35 U.S.C. §103(a) as unpatentable over Kim in view of Penners, and further in view of Russell. The Examiner states that Kim and Penners lack the teaching of living cells as therapeutic agents, and that this deficiency is cured by the teachings of Russell (Action at page 16). This rejection is traversed.

The merits of the combination of Kim and Penners, as proposed by the Examiner, are discussed above. In summary, one of ordinary skill in the art would find no motivation to combine the teachings of Penners with Kim, at least for the reason that the compositions of Penners would generate byproducts that are potentially toxic to the CNS and are therefore unsuitable for administration to the CSF.

Regardless of the therapeutic agents that are employed, the teachings of Russell do not provide the motivation that would be needed to combine the teachings of Kim with the teachings of Penners. Russell is directed to the treatment of leukemia using living cells as therapeutic agents. Russell does not address biocompatible compositions suitable for administration to the cerebrospinal fluid of a subject comprising a plurality of polymer particles as claimed. Therefore, Russell does not address the deficiencies of either Kim or Penners, or the combination of Kim with Penners as described above, with respect to claims 1 or 22 (and claims dependent thereon, including claims 36 and 39). Any combination of Russell with Kim or Penners (or both) fails to teach the claimed invention; accordingly, applicants respectfully request withdrawal of the rejection.

CONCLUSION

Applicants submit that the claims of the application are in condition for allowance. Applicants respectfully request withdrawal of the rejections, and prompt issuance of a notice of allowance. If the Examiner has any questions concerning this communication, or would like to discuss the application, the art, or other pertinent matters, a telephone call to the undersigned would be welcomed.

Respectfully submitted,

By: Reg. No. 45,409

Ingrid A. Beattie (Reg. No. 42,306)
Attorney for Applicants
c/o MINTZ, LEVIN, COHN, FERRIS, GLOVSKY, AND POPEO, P.C.
Telephone: (617) 542-6000
Customer No. 30623

Date: December 4, 2006

TRA 2222855v.1